Medical Progress

Current Status of Pancreas Transplantation

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Pancreas transplantation for the treatment of diabetes mellitus is being done with increasing frequency. Refined operative techniques, an improved immunosuppression regimen, and an earlier recognition of rejection have led to dramatic increases in both graft and patient survival rates. Preliminary data suggest that a functioning pancreatic allograft may arrest or reverse most of the complications of diabetes, although the effects on retinopathy remain controversial. Patients also acquire a strong sense of well-being after successful pancreas transplantation.

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Clinical pancreas transplantation for the treatment of diabetes mellitus is being used with increasing frequency. Between December 1966 and April 1987, a total of 1,157 pancreas transplants had been reported to the International Pancreas Transplant Registry, with 736 having been done since 1983.[1] The resolution of early technical problems and improved immunosuppression have enhanced graft survival. Morbidity and mortality rates have likewise been reduced.

A successful pancreas transplant achieves a more physiologic approach to the treatment of diabetes mellitus and may arrest the complications of diabetes. Patients also report a notable improvement in their sense of well-being.

Historical Aspects

Early investigation of the source and action of insulin led to the finding that a denervated pancreas allograft could autoregulate and maintain normoglycemia. Before the first clinical pancreas transplant in 1966, extensive experimental studies focused primarily on the technical aspects of transplantation.[2,3] A number of techniques were developed, and most were discarded. These early methods included partial pancreaticoduodenal allografts with external drainage and segmental and whole pancreas, duct-ligated allografts. Complications were frequent and included autodigestion, fistula formation, infection, and vascular thrombosis. There were no long-term successes. The present methods are now best classified as to whether segmental or whole organ transplantation is done and according to the method of exocrine secretion management.

Patient Selection and Evaluation

Most patients considered for pancreatic transplantation have type I (insulin-dependent) diabetes mellitus. Those who have had transplants fall into four groups: those with systemic complications such as retinopathy or neuropathy without renal involvement, patients without systemic complications of insulin-dependent diabetes but in whom metabolic control is difficult, patients with a previous kidney transplant, and those patients with end-stage renal disease and systemic complications who would benefit from simultaneous kidney and pancreatic transplants.[4-7]

Patients must be of a suitable age, generally 15 to 50, show ABO compatibility with a negative crossmatch, and lack physical evidence of far-advanced systemic complications such as gangrene of the lower extremities, severe gastroenteropathy, and significant coronary artery disease. Other contraindications to pancreas transplantation include the presence of active infections, malignancy, alcoholism or chemical dependency, and certain psychiatric illnesses.

All patients undergo extensive laboratory and physical examination including detailed neurologic, ophthalmologic, and cardiac evaluations. Because of the significant incidence of coronary artery disease in this patient population, considerable emphasis is placed on the cardiac evaluation. Most centers begin with noninvasive studies in asymptomatic patients and proceed to coronary angiography when results are positive or inconclusive. Some centers do angiograms on all candidates.[8,9] Abnormalities detected with coronary angiography may be treated with an angioplasty or coronary artery bypass graft before a pancreatic transplantation.

Donor Selection

In general, the criteria for selecting a pancreatic cadaver donor are similar to those used with kidney, heart, or liver donation. The donor must be clinically brain dead; be free of malignancy except primary brain tumors and possibly skin tumors; have no septic or chronic infectious process, hepatitis, or a positive titer for the human immunodeficiency virus; be younger than 60 years of age; and have no prolonged hypotension or asystole. In addition, other criteria specific for pancreas transplantation include no history of alcoholism or chemical dependency, no metabolic or endocrine-related coma, no evidence of intra-abdominal or pancreatic trauma, and normal pancreatic function with no family history of diabetes. Mild hyperamylasemia and hyperglycemia are not contraindications to pancreas donation since amylase and glucose levels may be elevated due to resuscitative efforts rather than pancreatic damage.

Immunologic advantages have led to the use of segmental grafts from living related donors. Sutherland and co-workers have defined specific criteria for living related donor selection. These include normal glucose tolerance indices; absent islet cell antibodies; a sum of the insulin values at 0, 60, 120, and 180 minutes during the cortisone-stimulated glucose tol-

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erance test of greater than 90 μU higher than the sum of corresponding values of the standard tests; and a sum of 1- and 3-minute insulin values during an intravenous glucose tolerance test of greater than 80 μU. Living related donors must also be at least ten years older than the recipient was when diabetes started, and the recipient must have had diabetes at least ten years before transplant. Using these criteria, Sutherland and associates have not reported abnormal results on oral glucose tolerance tests postoperatively or donor deaths.[7]

Pancreas Harvest and Preservation

The harvest and preservation of the pancreas is one of the most important aspects of transplantation. The transplant team must have a well-defined, systematic approach for retrieving more than one organ. To facilitate this, several techniques have been devised. Some involve meticulous dissection and isolation of each organ, while others stress an en bloc approach. To avoid excessive handling, which may aggravate graft edema and contribute to graft malfunction, a "no touch" technique of pancreatic harvest has been advocated.[8]

In most instances, the donor heart and kidneys are harvested concurrently. Procuring the liver, however, usually limits the procedure to segmental pancreas removal because the portal vein and celiac axis are used for both liver and whole pancreas transplantation. Modifications in technique may permit whole pancreas retrieval, but, in general, segmental grafts are harvested in liver donors.

A segmental graft consists of the tail and body of the pancreas based on a vascular pedicle of the splenic vessels or the portal vein and celiac axis. When the liver is harvested concurrently, the vascular pedicle is based solely on the splenic vessels. The whole pancreas graft is based on the portal vein, celiac axis, and superior mesenteric artery. In addition, a button of duodenum containing the papilla of Vater or the entire duodenum is harvested en bloc with the whole pancreas.

The pancreas is especially susceptible to warm ischemia. Cold perfusion usually with a Ringer's lactate solution is therefore initiated in situ after the aorta and inferior vena cava are cannulated or immediately after removal. Low-pressure perfusion with Collin's solution or a similar cold storage solution is continued ex vivo, and hypothermic storage (4°C) is maintained until transplantation.

Once in cold storage, the pancreas graft is prepared for transplantation. Lymphatics are ligated with fine sutures, the vessels are further dissected and prepared for anastomosis, and the exocrine duct is prepared.

The preservation time is optimally less than six hours. Cold storage of longer than 12 hours, however, has been compatible with normal graft function.[10] This relatively short storage does not allow for human leukocyte antigen typing. Recipient selection, therefore, is based on ABO compatibility.

Surgical Technique

Pancreas transplants may be categorized by whether a segmental or a whole organ graft is used. Classification is further defined by the site of transplantation and the method used to manage the exocrine duct.

Segmental grafts are commonly placed extraperitoneally or intraperitoneally in the pelvis with vascular anastomosis to the iliac vessels (Figure 1). The exocrine duct may be occluded with neoprene or drained into the jejunum or urinary bladder. Less common variations include drainage into the stomach and placing the graft in the groin with the duct occluded. Whole organ grafts are also placed in the pelvis using similar techniques. The most common forms of exocrine drainage are Roux-en-Y pancreaticojejunostomy (enteric drainage; Figure 2) and pancreaticocystostomy (bladder drainage; Figure 3).

Segmental grafts are more frequently used in Europe, constituting 90% of cases, while in North America 70% are whole organ transplants. Methods of duct management also vary. Urinary drainage accounts for about 70% of cases in North America and duct occlusion, usually with neoprene, 56% of cases in Europe.[1] The ideal pancreatic mass for transplantation and the best surgical technique remain controversial.[11] Further studies are necessary to elucidate these problems.

Immunosuppression

Agents currently used for immunosuppression and for the treatment of allograft rejection in pancreas transplantation include cyclosporine, azathioprine, prednisone, antithymocyte globulin, antilymphocyte globulin, and OKT3 or a similar monoclonal antibody.

The combination of prednisone and azathioprine was the mainstay of immunosuppression before the development of cyclosporine. Successful results were limited, however. The addition of cyclosporine enhanced graft survival.[12] Cyclosporine used alone achieves results comparable to the combination of azathioprine and prednisone, but when used in combination with azathioprine, prednisone, or both, the results are significantly improved.[10] Most current regimens use multidrug combinations, primarily triple-drug therapy with

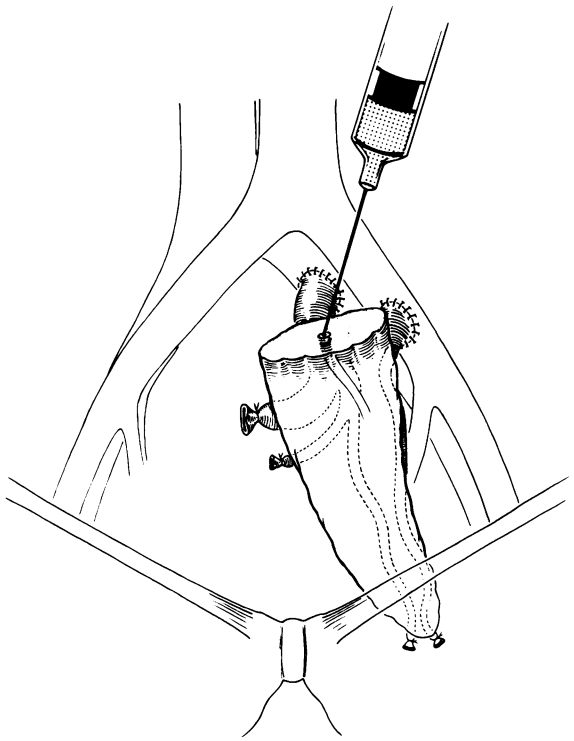

Figure 1.—A segmental pancreas allograft is shown with the occluded exocrine duct placed in the pelvis with vascular anastomosis to the iliac vessels.

cyclosporine, prednisone, and azathioprine. In addition, Sollinger and colleagues have reported a further improvement of graft survival by adding antilymphocyte globulin to the triple-drug regimen.[13] The synergistic effect noted with multidrug use allows the administration of lower doses of individual drugs, thus lowering the risks of detrimental effects. Immunosuppression may also be tailored to each patient to a certain degree.

As in renal transplantation, adjuvant methods of immunosuppression continue to be evaluated. A blood transfusion is often given preoperatively, although the benefits are not defined in pancreas transplantation. The donor spleen has been included with the pancreas allograft in an attempt to improve immunologic acceptance, but substantial graft-versus-host disease has resulted, and no immunologic benefit has been conclusively shown.[14-16] Other adjunctive measures that have been or are currently under investigation include selective depletion of passenger leukocytes in the allograft, recipient lymphoid irradiation, or splenectomy, plasma exchange, and thoracic duct drainage.[17-19]

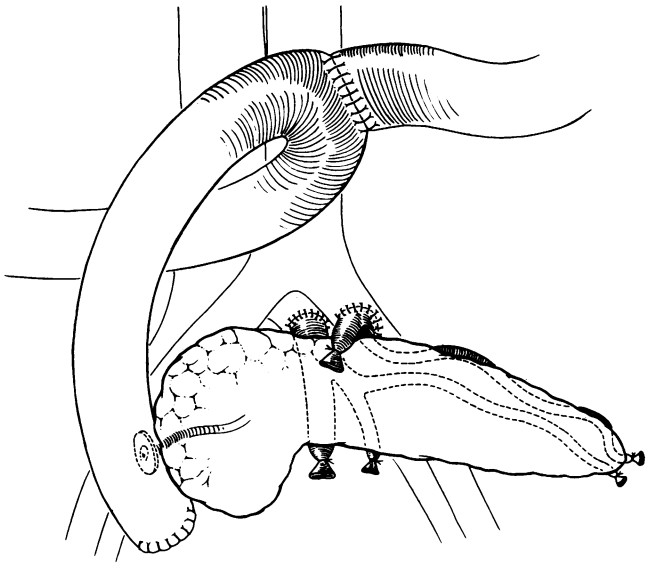

Figure 2.—A whole pancreas allograft is placed in the pelvis with Roux-en-Y duct drainage and vascular anastomosis to the iliac vessels.

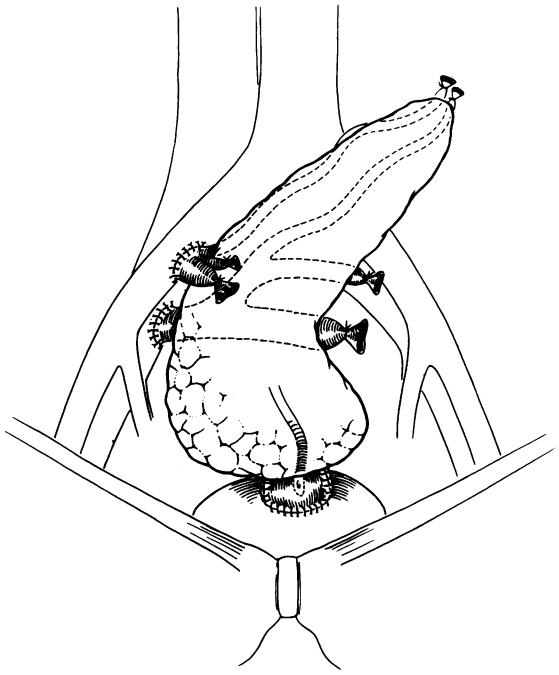

Figure 3.—A whole pancreas allograft is shown using pancreaticocystostomy with vascular anastomosis to the iliac vessels.

Rejection is most commonly treated with the pulsed administration of high doses of steroids or courses of antilymphocyte or antithymocyte globulin. Monoclonal antibodies such as OKT3 or similar agents are also used to treat primary rejection episodes, although many centers reserve their use for recurrent rejection.

Postoperative Management

A pancreas transplant recipient requires certain management considerations in addition to routine postoperative care. For example, a significant incidence (approximately 11%) of graft thrombosis and subsequent graft failure necessitates the use of anticoagulation in the postoperative period.[10] This is accomplished in many centers by the use of low-molecular-weight dextran, aspirin, or dipyridamole (or a combination of these) and may range to full anticoagulation with the administration of heparin followed by warfarin sodium.

Occasionally when a portion of duodenum is included with the whole pancreas graft and drained into the urinary bladder to facilitate exocrine drainage, a metabolic acidosis results due to bicarbonate loss. This may require maintenance bicarbonate supplements.[6]

In addition to these measures, some investigators think that graft survival is enhanced by "resting" the newly transplanted pancreas in the immediate postoperative period. Small doses of insulin are therefore given to keep plasma glucose levels at less than 8.3 mmol per liter (150 mg per dl) while the patient is receiving intravenous fluids.[7,9,20] Somatostatin may also be given to reduce graft edema and exocrine secretion.[9,21]

Antibiotics, usually second- or third-generation cephalosporins or a semisynthetic penicillin, are often administered perioperatively and for as long as five days after the operation. Nasogastric suction and a nothing-by-mouth status are maintained until the postoperative ileus resolves. If prolonged (longer than a week) ileus is expected or if nutritional deficiencies are evident, hyperalimentation is initiated.

Blood glucose levels are measured as frequently as hourly in the immediate postoperative period, and blood chemistry levels are measured daily. Glucose tolerance tests are done and metabolic profiles are determined as needed. Patients are instructed on monitoring their blood glucose, weight, and temperature at home and are observed as outpatients at least weekly in the immediate postoperative period.

Diagnosing Rejection

The recognition of rejection in a pancreas recipient is often difficult. The clinical findings of rejection, which include fever, graft tenderness, abdominal pain, ileus, malaise, and leukocytosis, are not consistently present and may be found with graft pancreatitis, recurrent disease, vascular thrombosis, and intra-abdominal infections. Furthermore, methods available to assist in the diagnosis of rejection may be limited by the type of exocrine management.

The mainstay of diagnosis has been an elevation of fasting serum glucose levels. Unfortunately, this is a relatively late

finding and in most patients with hyperglycemia, graft function continues to deteriorate despite antirejection therapy.[22] Exocrine function, however, has been shown to be a sensitive marker of graft rejection.[23,24] Using certain techniques of exocrine management, these secretions may be easily and reliably assessed. Enteric drainage techniques allow these secretions to be quantified, but more accurate daily determinations of amylase levels are made using the urinary bladder drainage technique. Reductions of urinary amylase levels measured by these techniques have been shown to correlate well with early graft rejection. Serum amylase levels, however, are difficult to interpret and are of little use in diagnosing rejection.[25]

Other means of recognizing pancreas graft rejection are being investigated. Various serum and urinary markers of graft function have been identified, although to date their use has met with limited success. Graft imaging techniques such as ultrasonography, nuclear magnetic resonance, and radionuclide scans may provide useful information, but they also require further refinement.

The most definitive method of diagnosing rejection in the pancreas graft is open biopsy. This, however, requires a surgical procedure that is associated with pancreatitis, leak, and fistula formation, creating significant risk for these patients. It is therefore infrequently done.

In a patient with a simultaneous kidney-pancreas transplant, the markers of kidney rejection precede those associated with pancreas rejection. Experimental studies have shown that mononuclear cell infiltration occurs simultaneously with rejection in both organs. Islet sparing is noted early in the course of rejection, however.[26] In most instances, elevations in blood urea nitrogen and creatinine values occur earlier than hyperglycemia. Prompt treatment following evidence of kidney rejection results in increased pancreatic graft survival.[13]

Results

The early results of pancreas transplantations were dismal. As recently as four years ago, the overall one-year rate of graft function was 23% and the associated three-month mortality rate 18%.[27] Improved immunosuppression, refined operative techniques, and the earlier diagnosis and treatment of rejection, however, have improved results dramatically. The rates of overall graft and patient survival reported to the pancreas transplant registry between 1983 and 1987 were 47% and 81%, respectively.[1]

Worldwide the number of segmental grafts far exceeds the number of whole organ transplants, while the three principal methods of duct management, occlusion and enteric and urinary drainage, enjoy equal popularity. Overall graft and patient survival rates for each method, however, show no statistical difference. A preservation time of less than six hours improves the rate of graft survival to a small but significant degree when compared with preservation times of more than six hours (46% versus 39%). Combination immunosuppression regimens with cyclosporine, azathioprine, and prednisone also are associated with a higher rate of graft survival when compared with using cyclosporine without azathioprine or azathioprine without cyclosporine. No detrimental effects on patient survival are noted with the multidrug protocols.[1,10]

Graft failure is most often due to rejection (40%), although technical problems, including a 10% to 15% incidence of vessel thrombosis, account for 20% to 25% of graft losses.[10] In addition, major complications including pancreatitis, fistula formation, exocrine leak, and infection occur in as many as 50% of patients. It is anticipated, however, that further improvements of technique and immunosuppression will lower the incidence of these problems.

Recently Sollinger and co-workers have reported overall graft and patient survival rates of 73.1% and 95.6%, respectively, at one year. They use whole organ grafts with urinary bladder drainage and quadruple-drug immunosuppression with prednisone, cyclosporine, azathioprine, and antilymphocyte globulin.[13] They believe that bladder drainage of exocrine secretions has led to these superior results because the use of this technique has resulted in fewer complications and has allowed for the earlier diagnosis and treatment of rejection. Similar results have been reported by others using this technique.[8,28]

With this improved graft survival, evidence is mounting that pancreas transplantation may lead to a reversal or arrest of the complications of diabetes. Serial biopsy specimens taken one to four years after simultaneous kidney-pancreas transplants show no renal diabetic changes, whereas kidneys transplanted alone in a diabetic patient may show diabetic nephropathy as early as 30 months after transplantation.[29] This suggests that a functioning pancreatic graft may prevent renal changes associated with diabetes. Nerve conduction studies have documented improvement after successful transplantations, and most patients have reported symptomatic improvement.[4-7,9,20,29-31] Visual acuity may also stabilize, although early results are inconclusive.[4-7,9,20,29,31] Prospective studies are underway to further evaluate the metabolic and physiologic effects of pancreas transplantation.

Conclusions

Graft survival rates now approach those of other solid organs, and other significant gains have been made. Surgical techniques have been refined, and combination immunosuppression has improved graft survival without adversely affecting patients' morbidity and mortality. As a result, the metabolic and physiologic benefits of pancreatic transplantation are being realized.

REFERENCES

1. Sutherland DER, Moudry KC: Pancreas transplantation: North American versus European experience. Transplant Proc 1987; 19:3867-3869

2. Kelly WD, Lillehei RC, Merkel FK, et al: Allotransplantation of the pancreas and duodenum along with the kidney in diabetic nephropathy. Surgery 1967; 61:827-837

3. Lillehei RC, Feemster JA, Idezuki Y, et al: Experimental pancreaticoduodenal preservation and transplantation. Surg Gynecol Obstet 1968; 126:1002-1014

4. Munda R, First MR, Weiss MA, et al: Pancreas transplantation—University of Cincinnati. Transplant Proc 1987; 19(suppl 4):17-23

5. Mittal VK, Toledo-Pereyra LH: Pancreas transplantation—The Detroit experience (Mount Carmel Mercy Hospital). Transplant Proc 1987; 19(suppl 4):24-28

6. Dafoe DC, Campbell DA Jr, Merion RM, et al: Pancreatic transplantation—University of Michigan. Transplant Proc 1987; 19(suppl 4):55-62

7. Sutherland DER, Goetz C, Najarian JS: Pancreas transplantation at the University of Minnesota: Donor and recipient secretion, operative and postoperative management and outcome. Transplant Proc 1987; 19(suppl 4):63-74

8. Corry RJ: University of Iowa experience in pancreatic transplantation. Transplant Proc 1987; 19(suppl 4):37-39

9. Land W, Landgraf R, Illner WD, et al: Clinical pancreatic transplantation using the prolamine duct occlusion technique—The Munich experience. Transplant Proc 1987; 19(suppl 4):75-83

10. Sutherland DER, Moudry KC: Pancreas transplant registry report. Transplant Proc 1987; 19(suppl 4):5-7

11. Dubernard JM, Gelet A, Faure JL, et al: Segmental or whole pancreatic graft? Further comparison of metabolic control between segmental pancreatic grafts and whole pancreas grafts in the long term. Transplant Proc 1987; 19:3872-3873

12. Sutherland DER, Goetz FC, Najarian JS: Improved pancreas graft survival

rates by use of multiple drug combination immunotherapy. Transplant Proc 1986; 18:1770-1773

13. Sollinger HW, Stratta RJ, Kalayoglu M, et al: Pancreas transplantation with pancreaticocystostomy and quadruple immunosuppression. Surgery 1987; 102:674-679

14. Schulak JA, Engelstad K: Splenectomy in experimental pancreas transplantation. Transplantation 1985; 40:564-566

15. Dafoe DC, Campbell DA Jr, Marks WH, et al: Association of inclusion of the donor spleen in pancreaticoduodenal transplantation with rejection. Transplantation 1985; 40:579-584

16. Sollinger H, Deierhoi M, Belzer F, et al: Lethal graft versus host disease in a recipient of pancreas-spleen transplantation. Transplantation 1986; 41:544-545

17. Du Toit D, Heydenrych JJ, Smit B, et al: Segmental pancreatic allograft survival in baboons treated with combined irradiation and cyclosporine: A preliminary report. Surgery 1985; 97:447-453

18. Stipa S, Fallucca F, Tersigni R, et al: Insulin, C-peptide, glucagon and somatostatin secretion in segmental pancreatic autotransplantation. Transplant Proc 1984; 16:741-744

19. Sollinger HW, Stratta RJ, Kalayoglu M, et al: The University of Wisconsin experience in pancreas transplantation. Transplant Proc 1987; 19(suppl 4):48-54

20. Bartos V, Vaněk I: Pancreatic transplantation in Czechoslovakia. Transplant Proc 1987; 19(suppl 4):84-85

21. Sells RA: Experience in pancreatic renal transplantation at Liverpool, UK. Transplant Proc 1987; 19(suppl 4):40-43

22. Sutherland DER, Kendall DM: Pancreas transplantation—Registry report and a commentary, *In* High-tech medicine (Special Issue). West J Med 1985; 143:845-852

23. Prieto M, Sutherland DER, Najarian JS, et al: Early diagnosis and treatment of rejection in pancreas transplantation. Transplant Proc 1986; 18:1805-1806

24. Sollinger HW, Cook K, Kamps D, et al: Clinical and experimental experience with pancreaticocystostomy and exocrine pancreatic drainage in pancreas transplantation. Transplant Proc 1984; 16:749-751

25. Sutherland DER, Goetz FC, Najarian JS: One hundred pancreas transplants at a single institution. Ann Surg 1984; 200:414-440

26. Severyn W, Olson L, Miller J, et al: Studies on the survival of simultaneous canine renal and segmental pancreatic allografts. Transplantation 1982; 33:606-612

27. Sutherland DER: Current status of pancreas transplantation: Registry statistics and an overview. Transplant Proc 1983; 15:1303-1307

28. Sutherland DER, Goetz FC, Najarian SS: Pancreas transplant results according to the technique of duct management: Bladder versus enteric drainage. Surgery 1987; 102:680-691

29. Groth CG, Östman J, Gunnarsson R, et al: Pancreatic transplantation with enteric exocrine diversion—The Stockholm experience. Transplant Proc 1987; 19(suppl 4):86-91

30. Margreiter R, Steiner E, Königsrainer A, et al: Pancreas transplantation—The Innsbruck experience. Transplant Proc 1987; 19(suppl 4):33-36

31. Schlumpf R, Largiadèr F, Decurtins M: Experience in clinical pancreas transplantation—University of Zürich. Transplant Proc 1987; 19(suppl 4):92-95